
Considerations in Demonstrating Interchangeability With a Reference Product

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Ebla Ali-Ibrahim, 301-796-3691, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)**

**January 2017
Biosimilars**

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Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
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5 This draft guidance, when finalized, will represent the current thinking of the Food and Drug
6 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not
7 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the
8 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible
9 for this guidance as listed on the title page.
10

11 I. INTRODUCTION

12 This guidance is intended to assist sponsors in demonstrating that a proposed therapeutic protein
13 product is interchangeable with a reference product for the purposes of submitting a marketing
14 application or supplement under section 351(k) of the Public Health Service Act (PHS Act) (42
15 U.S.C. 262(k)). The Biologics Price Competition and Innovation Act of 2009 (BPCIA Act)
16 amends the PHS Act and other statutes to create an abbreviated licensure pathway in section
17 351(k) of the PHS Act for biological products shown to be biosimilar² to or interchangeable with
18 an FDA-licensed biological reference product³ (see sections 7001 through 7003 of the Patient
19 Protection and Affordable Care Act (Affordable Care Act) (Public Law 111-148)). Although the
20 351(k) pathway applies generally to biological products, this guidance focuses on therapeutic
21 protein products and gives an overview of important scientific considerations in demonstrating
22 interchangeability of a proposed therapeutic protein product (*proposed interchangeable product*
23 or *proposed product*) with a reference product.
24

25 This guidance is one in a series of guidances that FDA is developing to implement the BPCIA Act
26 and includes references to information from other FDA guidances, where appropriate.
27

28 In general, FDA's guidance documents do not establish legally enforceable responsibilities.
29 Instead, guidances describe the Agency's current thinking on a topic and should be viewed only
30 as recommendations, unless specific regulatory or statutory requirements are cited. The use of
31

¹ This guidance has been prepared by the Office of Medical Policy in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

² Section 351(i)(2) of the PHS Act defines *biosimilar* or *biosimilarity* to mean that "the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components" (highly similar provision) and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product" (no clinically meaningful differences provision).

³ Section 351(i)(4) defines *reference product* to mean "the single biological product licensed under subsection (a) against which a biological product is evaluated in an application submitted under subsection (k)."

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36 the word *should* in Agency guidances means that something is suggested or recommended, but
37 not required.

38

39

40 II. BACKGROUND

41

42 Section 351(k) of the PHS Act, as amended by the BPCI Act, sets forth the requirements for an
43 application for a proposed biosimilar product and an application or a supplement for a proposed
44 interchangeable product. Section 351(k)(4) of the PHS Act further provides that upon review of
45 an application submitted under section 351(k) or any supplement to such an application, FDA
46 will determine the biological product to be interchangeable with the reference product if FDA
47 determines that the information submitted in the application or the supplement is sufficient to
48 show that the biological product “is biosimilar to the reference product” and “can be expected to
49 produce the same clinical result as the reference product in any given patient”⁴ and that “for a
50 biological product that is administered more than once to an individual, the risk in terms of
51 safety or diminished efficacy of alternating or switching between use of the biological product
52 and the reference product is not greater than the risk of using the reference product without such
53 alternation or switch.”⁵

54

55 Section 351(i) of the PHS Act states that the term *interchangeable* or *interchangeability*, in
56 reference to a biological product that is shown to meet the standards described in section
57 351(k)(4) of the PHS Act, means that “the biological product may be substituted for the
58 reference product without the intervention of the health care provider who prescribed the
59 reference product.”⁶

60

61

62 III. GENERAL PRINCIPLES

63

64 FDA intends to consider the totality of the evidence provided by a sponsor when the Agency
65 evaluates the sponsor’s demonstration of interchangeability according to the criteria set forth in
66 section 351(k).

67

68 To support a demonstration of interchangeability, section 351(k)(4)(A) of the PHS Act provides,
69 among other things, that a sponsor must show that the proposed product “is biosimilar to the
70 reference product.” Where a product is first licensed as a biosimilar, that licensure may be
71 referenced to support a showing for this statutory criterion for demonstrating interchangeability.

72

73 In addition, section 351(k)(4)(A) of the PHS Act provides that an application for an
74 interchangeable product must include information sufficient to show that the proposed
75 interchangeable product “can be expected to produce the same clinical result as the reference

⁴ Section 351(k)(4)(A) of the PHS Act.

⁵ Section 351(k)(4)(B) of the PHS Act.

⁶ The terms *interchangeable* or *interchangeability* in this guidance have the same meaning as defined in section 351(i)(3) of the PHS Act.

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76 product in any given patient.” FDA expects that sponsors will submit data and information to
77 support a showing that the proposed interchangeable product can be expected to produce the
78 same clinical result as the reference product in all of the reference product’s licensed conditions
79 of use. The data and information to support a showing that the proposed interchangeable product
80 can be expected to produce the same clinical result as the reference product in all of the reference
81 product’s licensed conditions of use may vary depending on the nature of the proposed
82 interchangeable product and may include, but need not be limited to, an evaluation of data and
83 information generated to support a demonstration of a biological product’s biosimilarity, such as:
84

- 85 • The identification and analysis of the critical quality attributes
- 86 • The identification of analytical differences between the reference product and the
87 proposed interchangeable product, and, in addition, an analysis of the potential clinical
88 impact of the differences
- 89 • An analysis of mechanism(s) of action in each condition of use for which the reference
90 product is licensed, which may include the following:
 - 91 – The target receptor(s) for each relevant activity/function of the product
 - 92 – The binding, dose/concentration response, and pattern of molecular signaling upon
93 engagement of target receptor(s)
 - 94 – The relationship between product structure and target/receptor interactions
 - 95 – The location and expression of target receptor(s)
- 96 • The pharmacokinetics and biodistribution of the product in different patient populations
- 97 • The immunogenicity risk of the product in different patient populations
- 98 • Differences in expected toxicities in each condition of use and patient population
99 (including whether the expected toxicities are related to the pharmacological activity of
100 the product or to off-target activities)
- 101 • Any other factor that may affect the safety or efficacy of the product in each condition of
102 use and patient population for which the reference product is licensed

103 Where applicable, the data and information should include a scientific justification as to why any
104 differences that exist between the reference product and the proposed interchangeable product,
105 with respect to the factors described, do not preclude a showing that the proposed
106 interchangeable product can be expected to produce the same clinical result as the reference
107 product in any given patient. As previously noted, the data and information may vary depending
108 on the nature of the proposed interchangeable product, and not all factors will necessarily be
109 relevant to a given scientific justification. The data and information may also include a scientific
110 rationale to extrapolate data and information supporting a demonstration of interchangeability in
111 an appropriate condition of use to the remaining conditions of use for which the reference
112 product is licensed. Extrapolation of data is further described in section VI.B of this guidance.
113 Generally, the data and information to support a showing under the “can be expected to produce

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114 the same clinical result as the reference product in any given patient” standard will likely not
115 involve additional clinical studies other than those necessary to support other elements of
116 demonstrating interchangeability. We note that although a sponsor may seek licensure for a
117 proposed interchangeable product for fewer than all conditions of use for which the reference
118 product is licensed, we recommend that a sponsor seek licensure for all of the reference
119 product’s licensed conditions of use when possible.

120
121 In addition, section 351(k)(4)(B) of the PHS Act provides that another of the criteria for FDA to
122 make a determination of interchangeability is a finding that information in the application is
123 sufficient to show that “for a biological product that is administered more than once to an
124 individual, the risk in terms of safety or diminished efficacy of alternating or switching between
125 use of the biological product and the reference product is not greater than the risk of using the
126 reference product without such alternation or switch.” FDA expects that applications generally
127 will include data from a switching study or studies⁷ in one or more appropriate conditions of use.
128 FDA anticipates that data and information acquired from a switching study or studies will be
129 useful in assessing the risk, in terms of safety and diminished efficacy, of alternating or
130 switching between the products. Considerations for the design of a switching study, including
131 study endpoints, study design and analysis, study population, condition(s) of use, and routes of
132 administration to be studied, are discussed in detail in section VI.A of this guidance.

133
134 An interchangeable product may be substituted for the reference product without the intervention
135 of the health care provider who prescribed the reference product.⁸ Sponsors of proposed
136 interchangeable products should evaluate the proposed product’s presentation, including product
137 design and user interface, relative to the reference product. Considerations for developing
138 presentations, container closure systems, and delivery device constituent parts for proposed
139 interchangeable products are discussed in detail in section VIII of this guidance.

140

141

IV. SCOPE

142 This guidance provides an overview of important scientific considerations in demonstrating
143 interchangeability with a reference product, including the following:

144

- 145 • Data and information needed to support a demonstration of interchangeability
- 146 • Considerations for the design and analysis of a switching study or studies to support a
147 demonstration of interchangeability
- 148 • Recommendations regarding the use of a U.S.-licensed reference product in a switching
149 study or studies

150

⁷ The term *switching study or studies* as used throughout this guidance refers to a clinical study or studies used to determine the impact of alternating or switching between the proposed interchangeable product and the reference product.

⁸ Section 351(i) of the PHS Act.

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- Considerations for developing presentations, container closure systems, and delivery device constituent parts for proposed interchangeable products^{9,10}

V. FACTORS IMPACTING THE TYPE AND AMOUNT OF DATA AND INFORMATION NEEDED TO SUPPORT A DEMONSTRATION OF INTERCHANGEABILITY

The data and information needed to support a demonstration of interchangeability, beyond that needed to demonstrate biosimilarity,¹¹ may be dependent on and influenced by multiple factors, which are discussed in this section.

A. Product-Dependent Factors That May Impact the Data Needed to Support a Demonstration of Interchangeability

1. Product Complexity and the Extent of Comparative and Functional Characterization

Consistent with the guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*, the Agency recommends that sponsors use a stepwise approach generating data and information to address residual uncertainty about demonstrating interchangeability during product development. At each step, the sponsor should evaluate the extent to which there is residual uncertainty about the interchangeability of the proposed product with the reference product, and identify next steps to try to address that uncertainty.

Section 351(k)(4)(A)(i) of the PHS Act provides that one of the criteria for FDA to make a determination of interchangeability is a finding that information in the application is sufficient to

⁹ Products that include both a biological product and a device constituent part to deliver the biological product are combination products (see 21 CFR parts 3 and 4). The delivery device constituent part and the biological product constituent part may be a single entity (e.g., a prefilled syringe) or the two constituent parts may be co-packaged (e.g., a biologic in a vial packaged in the same box with a syringe). The primary mode of action of these combination products is provided by the biological product constituent part, which is regulated by CDER or CBER. CDER or CBER, therefore, will have primary jurisdiction for these combination products; and these Centers and the Center for Devices and Radiological Health (CDRH) will coordinate as appropriate.

¹⁰ Considerations specific to demonstrating interchangeability under section 351(k)(4) of the PHS Act with respect to container closure systems and delivery device constituent parts are addressed in section VIII of this guidance. This guidance does not address other information generally necessary to support the proposed container closure system and/or the delivery device constituent part of a proposed product. Sponsors should also refer to relevant FDA guidance documents and resources from CBER, CDRH, CDER, and the Office of Combination Products (OCP) to assess what other data and information should be included to support the proposed container closure system(s) and/or delivery device constituent part(s). (Some of the FDA guidances and other resources that address these topics are referenced at appropriate places in section VIII of this guidance.)

¹¹ Data and information needed to demonstrate biosimilarity are discussed in section VII of the guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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182 show that the proposed interchangeable product is biosimilar to the reference product. Such
183 information would include, in part, a showing that the proposed interchangeable product meets
184 the *highly similar* standard for demonstrating biosimilarity.¹² FDA acknowledges that there is a
185 continuum of comparative analytical data that could support a demonstration that the highly
186 similar standard is satisfied.¹³ For example, a fingerprint-like characterization¹⁴ may reduce
187 residual uncertainty regarding interchangeability and inform the data and information needed to
188 support a demonstration of interchangeability, which may lead to a more selective and targeted
189 approach to clinical studies necessary to demonstrate interchangeability.
190

191 Despite significant improvements in analytical techniques, current analytical methodologies may
192 not detect or characterize all relevant structural and functional differences between the reference
193 product and the proposed interchangeable product.¹⁵ There may also be some structural features
194 that specifically impact interchangeability (e.g., features that influence patient response to one
195 product after exposure to another product). Data sets that include highly sensitive analytics
196 and/or sequential analytical methods that can identify molecules with different combinations of
197 attributes (e.g., charge variants and glycoforms), as well as a comprehensive assessment of the
198 relationships between attributes, may provide information that reduces the residual uncertainty
199 about interchangeability and thus inform the data and information needed to support a
200 demonstration of interchangeability between the two products.
201

202 The extent to which data and information provided by these advanced analytical approaches
203 helps to reduce residual uncertainty about interchangeability depends on the degree of analytical
204 similarity between the products and the strength of the evidence for the clinical relevance of the
205 analytical data. Evidence of clinical relevance may range from a risk assessment describing the
206 potential importance of the additional attributes evaluated to advanced modeling supported by
207 functional and/or in vivo data. A clinically relevant and thus meaningful fingerprint-like
208 characterization may reduce residual uncertainty regarding interchangeability and may lead to a
209 more selective and targeted approach to the clinical studies necessary to demonstrate
210 interchangeability.
211

¹² Section 351(i)(2) of the PHS Act defines *biosimilarity*, in part, to mean “that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components.”

¹³ See the guidance for industry *Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product* for the Agency’s current thinking on factors to consider when demonstrating that a proposed therapeutic protein product is *highly similar* to a reference product.

¹⁴ For information regarding fingerprint-like characterization, see the guidance for industry *Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product*. Also see the draft guidance for industry *Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product*. When final, this guidance will represent the Agency’s current thinking on this topic. Also see Kozlowski S, Woodcock J, Midthun K, Sherman RB, 2011, Developing the Nation’s Biosimilars Program, *N Engl J Med*, 365:385–388.

¹⁵ See Section IV.A. Nature of Protein Products and Related Scientific Considerations in the guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*.

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212 The product's degree of structural and functional complexity may also influence the data and
213 information needed to support a demonstration of interchangeability, because the product's
214 structural complexity can affect the residual uncertainty regarding interchangeability. For
215 example, products expected to have a single target (e.g., a receptor) may have less residual
216 uncertainty regarding interchangeability than those acting on multiple or less-defined biological
217 pathways.

218
219 Along the continuum of possible data sets that could support a demonstration of the highly
220 similar standard, there may be extensive characterization approaches that have some, but not all,
221 of the features of a meaningful fingerprint-like characterization. These approaches could be of
222 greater importance for more-complex products because these products would have a larger
223 number of attributes and thus a potential for greater residual uncertainty regarding
224 interchangeability. Such extensive characterization approaches may reduce the residual
225 uncertainty regarding interchangeability for complex products. Reducing residual uncertainty
226 can impact what additional data and information would be needed to support a demonstration of
227 interchangeability.

228
229 2. *Product-Specific Immunogenicity Risk*

230
231 Clinical experience with the reference product and comprehensive product risk assessments (e.g.,
232 regarding immunogenicity)¹⁶ may also affect the data and information needed to support a
233 demonstration of interchangeability. For example, products with a documented history of
234 inducing detrimental immune responses may require more data to support a demonstration of
235 interchangeability than products with an extensive documented history that immunogenicity does
236 not impact clinical outcomes.

237
238 3. *Totality of Factors to Consider in Assessing the Data and Information Needed to*
239 *Support a Demonstration of Interchangeability*

240
241 The factors discussed in sections V.A.1 and V.A.2 of this guidance need to be considered
242 together to inform a consideration regarding residual uncertainty about the data and information
243 needed to support a demonstration of interchangeability. Consider the following illustrative
244 examples:

245
246 • Product A has relatively low structural complexity, has been demonstrated to have
247 meaningful fingerprint-like analytical similarity to the reference product as a part of
248 demonstrating biosimilarity, and has a low incidence of serious adverse events related to
249 immunogenicity. Here, data derived from an appropriately designed switching study (see
250 section VI.A) may be sufficient to support a demonstration of interchangeability.

251 • Product B has high structural complexity, has been demonstrated to be highly similar to
252 the reference product as a part of demonstrating biosimilarity but has no demonstration of
253 meaningful fingerprint-like analytical similarity, and has known serious adverse events
254 related to immunogenicity. Here, postmarketing data for the product as a licensed

¹⁶ Section VII.D.2 in the guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* provides a discussion on clinical immunogenicity assessment.

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255 biosimilar, in addition to an appropriately designed switching study (see section VI.A),
256 may provide additional data and information necessary to support a demonstration of
257 interchangeability. The collection of biosimilar postmarketing data is described further in
258 section V.B of this guidance.

259 Based on the factors discussed in sections V.A.1 and V.A.2, the residual uncertainty regarding
260 the interchangeability of the respective proposed products (described in the preceding examples)
261 would be different. Therefore, the data and information necessary to support a demonstration of
262 interchangeability needs to be considered on a case-by-case basis.

B. Biosimilar Product Postmarketing Data That May Impact the Data Needed 264 to Support a Demonstration of Interchangeability

265 New tools and improved epidemiological approaches to evaluating postmarketing exposures and
266 outcomes lend promise to the continued improvement of the capabilities of postmarketing
267 surveillance and the collection of data related to the actual use of drug products in general.
268 However, our current thinking is that postmarketing data collected from products first licensed
269 and marketed as a biosimilar, without corresponding data derived from an appropriately
270 designed, prospective, controlled switching study or studies, generally would not be sufficient to
271 support a demonstration of interchangeability. For example, we generally would not expect
272 postmarketing data to provide sufficient information related to the impact on clinical
273 pharmacokinetics (PK) and pharmacodynamics (PD) of switching or alternating between the use
274 of the proposed interchangeable product and the reference product, which we think are important
275 study endpoint considerations in the switching studies for the reasons described in section VI.A.1
276 of this guidance.

277 Notwithstanding these limitations, however, we recognize that in certain circumstances,
278 postmarketing data from a licensed biosimilar product may be helpful as a factor when
279 considering what data is necessary to support a demonstration of interchangeability. For
280 example, some postmarketing data may describe the real-world use of the biosimilar product,
281 including certain safety data related to patient experience with some switching scenarios. Such
282 data may impact residual uncertainty about interchangeability and thus the data needed to
283 support a demonstration of interchangeability.

284 In certain situations, postmarketing surveillance data from the licensed biosimilar product in
285 addition to data from an appropriately designed switching study may be needed to address
286 residual uncertainty regarding a demonstration of interchangeability and add to the totality of the
287 evidence to support a demonstration of interchangeability. Further, there may be situations
288 where a postmarketing study, in addition to postmarketing surveillance data, from the licensed
289 biosimilar product may be needed to address residual uncertainty regarding a demonstration of
290 interchangeability. For example, as a scientific matter, where there is residual uncertainty
291 regarding interchangeability based on immunogenicity-related adverse events that could affect
292 use of the product as an interchangeable, a sponsor may need to first obtain licensure as a
293 biosimilar product and collect postmarketing data before interchangeability can be demonstrated.
294 In such cases, the type and amount of biosimilar product postmarketing data needed would
295 depend on the residual uncertainty regarding the demonstration of interchangeability. Sponsors
296 are encouraged to discuss with FDA their plans for the use of postmarketing data to address
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301 residual uncertainty about interchangeability and add to the totality of the evidence to support a
302 demonstration of interchangeability.

303

304

305 **VI. DATA AND INFORMATION NEEDED TO SUPPORT A DEMONSTRATION OF**
306 **INTERCHANGEABILITY**

307

308 FDA advises sponsors intending to develop a proposed interchangeable product to meet with
309 FDA to discuss their proposed product development plan. Early discussions with FDA about
310 product development plans, including adequate scientific justification for the proposed
311 development program, will facilitate development of interchangeable products.¹⁷

312

313 **A. Considerations for the Design and Analysis of a Switching Study or Studies**
314 **Needed to Support a Demonstration of Interchangeability**

315

316 For biological products that are intended to be administered to an individual more than once,
317 sponsors generally will be expected to conduct a switching study or studies to address the
318 statutory provision “for a biological product that is administered more than once to an individual,
319 the risk in terms of safety or diminished efficacy of alternating or switching between use of the
320 biological product and the reference product is not greater than the risk of using the reference
321 product without such alternation or switch” set forth in section 351(k)(4)(B) of the PHS Act.
322 The main purpose of a switching study or studies is to demonstrate that the risk in terms of safety
323 or diminished efficacy of alternating or switching between use of the proposed interchangeable
324 product and the reference product is not greater than the risk of using the reference product
325 without such alternation or switch. A switching study or studies should evaluate changes in
326 treatment that result in two or more alternating exposures (switch intervals) to the proposed
327 interchangeable product and to the reference product.

328

329 For biological products that are not intended to be administered to an individual more than once,
330 FDA expects that switching studies would generally not be needed. However, FDA expects that
331 a sponsor will provide a justification for not needing data from a switching study as a part of the
332 demonstration of interchangeability, and sponsors are encouraged to meet with FDA to discuss
333 their planned development approach.

334

335 Design of switching studies may be informed by how the proposed interchangeable product will
336 be used in clinical practice, taking into consideration scenarios where alternating or switching
337 products might cause the most clinical concern. For treatments that have a long course of
338 therapy, sponsors should anticipate dropouts in the study and should use a scientifically
339 justifiable method to address the increased possibility of missing data.

340

341 It is important to note that if patients experience an immune response or adverse event during the
342 course of a switching study, a carryover effect may make it difficult to determine whether the
343 proposed interchangeable product or the reference product caused the event. If an apparent

¹⁷ See the guidance for industry *Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants*, which provides recommendations to industry on all formal meetings between the FDA and sponsors or applicants for biosimilar biological products intended to be submitted under 351(k) of the PHS Act.

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344 difference in immune response or adverse events is noticed between the switching and non-
345 switching arms of the study (see section VI.A.2.a of this guidance), it would raise concerns as to
346 whether the proposed interchangeable product is interchangeable, regardless of whether the
347 proposed interchangeable product or the reference product or the switching of the two products
348 actually caused the event.

349
350 FDA has outlined a flexible approach regarding the design of any necessary switching study.
351 FDA will address program-specific scientific matters (e.g., the impact of small patient
352 populations) on a case-by-case basis in interactions with sponsors. To facilitate development of
353 interchangeable products, FDA encourages sponsors to have early discussions with FDA about
354 their product development plans.

355
356 1. *Study Endpoints*
357
358 The primary endpoint in a switching study or studies should assess the impact of switching or
359 alternating between use of the proposed interchangeable product and the reference product on
360 clinical pharmacokinetics and pharmacodynamics (if available), because these assessments are
361 generally most likely to be sensitive to changes in immunogenicity and/or exposure that may
362 arise as a result of alternating or switching. FDA recommends that clinical PK and PD test
363 methods and assays be developed and validated early in product development. The validation
364 should consider both the proposed interchangeable product and the reference product. Although
365 assessments of efficacy endpoints can be supportive, at therapeutic doses many clinical efficacy
366 outcomes would only be sensitive to large changes in exposure or immunogenicity, which may
367 not be observed in a study of limited duration and with a limited number of switches.

368
369 Biologically relevant PD measures, if available, may be useful as shorter-term, more-sensitive
370 indicators of the potential impact of alternating or switching on the risk of diminished efficacy as
371 compared to efficacy endpoints. Relevant PD measures may also be useful to reflect multiple
372 domains of activity, which could reduce residual uncertainty about interchangeability. Selection
373 of PD endpoints should be scientifically justified for the intended purpose. When PD endpoints
374 that are sensitive to changes in drug concentration can be identified, PD analysis, in addition to
375 PK analysis, may be useful to address residual uncertainty with respect to interchangeability.

376
377 In addition to PK and PD parameters, a switching study or studies would also be expected to
378 assess immunogenicity and safety.

379
380 2. *Study Design and Analysis*
381
382 a. *Dedicated Switching Study Design*
383
384 A study with a lead-in period of treatment with the reference product, followed by a randomized
385 two-arm period—with one arm incorporating switching between the proposed interchangeable
386 product and the reference product (switching arm) and the other remaining as a non-switching
387 arm receiving only the reference product (non-switching arm)—may be appropriate when
388 designing a switching study. Considerations for the design and analysis of such a study are
389 discussed as follows:

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391 • Sample size: The sample size of the switching study should generally be based on PK
392 considerations (inter-subject variability in AUC_{tau} or C_{max} should be primary
393 considerations) and should be appropriately justified. As the switching study will likely
394 require repeated patient monitoring, the study designers should anticipate the possibility
395 of a considerable dropout rate for reasons unrelated to the study treatment arms. An
396 anticipated high dropout rate due solely to an influence affecting all treatment arms could
397 be assumed to be random. The negative impact on the statistical power of such a random
398 influence could be precluded by factoring such influences into the sample size
399 calculation. It should be noted that dropout rates or missing data rates that differentially
400 affect the study treatment arms could represent treatment arm differences, and sponsors
401 should provide adequate justification to FDA about any such differences and their
402 possible causes. In addition, FDA will investigate possible causes of the noted
403 differences in treatment arms.

404

405 • Number and duration of switches: The number and duration of switches between the
406 reference product and the proposed interchangeable product should take into
407 consideration the clinical condition to be treated, the therapeutic dosing of the product,
408 and the duration of the exposure interval to each product that would be expected to cause
409 the greatest concern in terms of immune response and resulting impact on safety and
410 efficacy, if any.

411

412 – The lead-in period should be of sufficient duration to ensure an adequate baseline
413 with respect to the study (e.g., steady state of pharmacokinetics) before randomization
414 to the switching period of the study.

415

416 – The switching arm is expected to incorporate at least two separate exposure periods to
417 each of the two products (i.e., at least three switches with each switch crossing over to the
418 alternate product).

419

420 – The last switching interval should be from the reference product to the proposed
421 interchangeable product, where the duration of exposure to the proposed
422 interchangeable product after the last switch is sufficiently long to allow for washout
423 of the reference product (i.e., at least three or more half-lives) to assess the
424 pharmacokinetics of the proposed interchangeable product in the switching arm and
425 compare it to the pharmacokinetics of the reference product in the non-switching arm.

426

427 • PK, PD, and immunogenicity sampling: To capture the full PK profile, intensive PK
428 sampling should be performed during the last switch interval following the dose after
429 which at least three half-lives of the reference product have elapsed. Trough PK
430 sampling should be conducted after each switch to ensure that steady state is attained.
431 The timing of PD¹⁸ and immunogenicity¹⁹ sampling should be appropriately justified.

¹⁸ See Section IV.H. Defining the Appropriate Pharmacodynamic Time Profile in the draft guidance for industry *Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product*. When final, this guidance will reflect FDA's current thinking on this topic.

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432

- 433 • Study Analysis:

434

- 435 – Primary analysis: The following PK data obtained during the intensive sampling
436 interval should be reported: C_{max} , T_{max} , C_{trough} , and AUC_{tau} . The log-transformed
437 AUC_{tau} and C_{max} data should be statistically analyzed using an analysis of the
438 variance. The 90% confidence interval for the geometric mean ratio of AUC_{tau} and
439 C_{max} between the proposed interchangeable product and the reference product should
440 be within 80–125%. C_{trough} and T_{max} should also be analyzed as secondary endpoints.
441 PD endpoints, when evaluated, should be measured at appropriate times during the
442 PK sampling interval.
- 443 – Safety, immunogenicity, and efficacy should be descriptively analyzed as secondary
444 endpoints.

445

- 446 b. Integrated Study Design

447

448 If a sponsor is considering a study design using a single study intended to (1) support a
449 demonstration of no clinically meaningful differences between the reference product and the
450 proposed product for biosimilarity²⁰ and (2) evaluate the impact of switching or alternating
451 between the reference product and the proposed product for interchangeability, an integrated,
452 two-part study design may be appropriate. Following the time point(s) for evaluation of the
453 appropriate endpoint(s) to support the demonstration of no clinically meaningful differences for
454 biosimilarity between the proposed product and the reference product in the first part of the
455 study, the subjects in the reference product arm should be re-randomized in the second part of
456 the study to continue to receive the reference product (non-switching reference product arm) or
457 to switch to the proposed product (switching arm) as described in section VI.A.2.a of this
458 guidance. FDA recommends continuing the proposed product arm (non-switching proposed
459 product arm) from the inception of the study, through the duration of the switching portion of the
460 integrated study, to the completion of the study.

461

462 An integrated study needs to be adequately powered to evaluate the appropriate endpoint(s) to
463 support the demonstration of no clinically meaningful differences for biosimilarity, where the
464 primary comparison is between the proposed product arm and the reference product arm. In
465 addition, the study needs to be adequately powered to evaluate pharmacokinetics and
466 pharmacodynamics (if available), following the last switch to support a demonstration of
467 interchangeability, where the primary comparison is between the switching arm and the non-
468 switching reference product arm.

469

470

¹⁹ See Section VII.A. Obtaining Patient Samples in the draft guidance for industry *Assay Development for Immunogenicity Testing of Therapeutic Proteins*. Also see Section IV. Recommendations for Mitigating Immunogenicity Risk in the Clinical Phase of Development of Therapeutic Protein Products in the guidance for industry *Immunogenicity Assessment of Therapeutic Protein Product*.

²⁰ Data and information needed to demonstrate biosimilarity are discussed in section VII of the guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*.

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471 3. *Study Population*

472
473 The study population for switching studies should be adequately sensitive to allow for detection
474 of differences in pharmacokinetics and/or pharmacodynamics, common adverse events, and
475 immunogenicity between the switching and non-switching arms. Even though it is likely that the
476 study population will generally have characteristics that are consistent with those of the
477 population studied for licensure of the reference product for the same indication, sponsors may
478 conduct switching studies in a patient population that is different from that used to support
479 licensure of the reference product. Sponsors should provide adequate scientific justification to
480 support that such a population is adequately sensitive to detect the impact of switching (e.g.,
481 differences in clinical pharmacokinetics and/or pharmacodynamics, common adverse events, and
482 immunogenicity).

483
484 FDA strongly recommends that sponsors use patients in switching studies because these studies
485 are designed to mimic how the proposed interchangeable product will be used in clinical
486 practice. In a circumstance where a sponsor considers using healthy subjects, the sponsor should
487 weigh the benefit of exposing healthy subjects to a proposed interchangeable product during the
488 course of a clinical study against the risk of having them develop antibodies to the product,
489 which in turn may preclude them from being able to receive the treatment in the future, if
490 needed. However, there may be some limited situations where it is clinically and ethically
491 appropriate to use healthy subjects in switching studies. Sponsors are strongly encouraged to
492 discuss with FDA their rationale for conducting switching studies in healthy subjects before
493 initiating studies, preferably before submitting a proposed protocol or protocol amendment.

494
495 4. *Condition of Use To Be Studied*

496
497 As described in section VI.B of this guidance, sponsors should consider choosing a condition of
498 use that would support subsequent extrapolation of data to other conditions of use.

499
500 In addition, it is important to note that a sponsor may obtain licensure only for a condition of use
501 (or uses) for which the reference product is licensed. If a reference product has multiple
502 conditions of use and one of those conditions of use was licensed under section 506(c) of the
503 Federal Food, Drug, and Cosmetic Act and 21 CFR part 601, subpart E (accelerated approval),
504 and the reference product's clinical benefit in this condition of use has not yet been verified in
505 postmarketing studies, then sponsors should consider studying another condition of use for
506 which the reference product is licensed, to avoid complications in the event that postmarketing
507 studies fail to verify the reference product's clinical benefit for the condition of use being
508 considered under the accelerated approval provisions.

509
510 5. *Route of Administration*

511
512 If a product is approved for more than one route of administration, sponsors should study the
513 route of administration that will best assess how a patient's immune response will impact the
514 clinical performance of the proposed interchangeable product, including changes in safety risk
515 and efficacy. Choosing a more immunogenic route of administration (e.g., subcutaneous rather

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516 than intravenous) for use in switching studies may help sponsors anticipate the clinical
517 implications of real-world use in clinical practice.

518

B. Extrapolation of Data

520

521 If the proposed product meets the statutory requirements for licensure as an interchangeable
522 product under section 351(k) of the PHS Act based on, among other things, data and information
523 sufficient to demonstrate interchangeability in an appropriate condition of use, the sponsor may
524 seek licensure of the proposed product as an interchangeable product for one or more additional
525 conditions of use for which the reference product is licensed. The sponsor would need to
526 provide sufficient scientific justification for extrapolating data to support a determination of
527 interchangeability for each condition of use for which the reference product is licensed and for
528 which licensure as an interchangeable product is sought. The scientific justification for
529 extrapolation should address, for example, the following issues for the tested and extrapolated
530 conditions of use:

531

- 532 • The mechanism(s) of action in each condition of use for which the reference product is
533 licensed, which may include the following:
 - 534 – The target receptor(s) for each relevant activity/function of the product
 - 535 – The binding, dose/concentration response, and pattern of molecular signaling upon
536 engagement of target receptor(s)
 - 537 – The relationship between product structure and target/receptor interactions
 - 538 – The location and expression of target receptor(s)
- 539 • The pharmacokinetics and biodistribution of the product in different patient populations
540 (Relevant PD measures may also provide important information on the mechanism(s) of
541 action.)
- 542 • The immunogenicity risk of the product in different patient populations
- 543 • Differences in expected toxicities in each condition of use and patient population
544 (including whether the expected toxicities are related to the pharmacological activity of
545 the product or to off-target activities)
- 546 • Any other factor that may affect the safety or efficacy of the product in each condition of
547 use and patient population for which the reference product is licensed²¹

548 Differences between conditions of use with respect to the factors described do not necessarily
549 preclude extrapolation. A scientific justification should address these differences in the context
550 of the totality of the evidence supporting a demonstration of interchangeability. Advanced

²¹ These factors are also discussed in Section VII.D.4. Extrapolation of Clinical Data Across Indications in the guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*.

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551 structural and functional characterization may also provide additional support for the justification
552 for extrapolation.

553
554 In choosing a condition of use to study that would permit subsequent extrapolation of data to
555 other conditions of use, FDA recommends that a sponsor consider choosing a condition of use
556 that would be adequately sensitive to assess the risk of alternating or switching between the
557 products, in terms of safety or diminished efficacy, in a switching study and subsequently
558 support extrapolation based on the factors described in this section.

559

560

561 VII. USE OF A U.S.-LICENSED REFERENCE PRODUCT IN A SWITCHING STUDY 562 OR STUDIES

563

564 In the context of demonstrating biosimilarity to a reference product, FDA has advised that
565 “sponsors may seek to use data derived from animal or clinical studies comparing a proposed
566 product with a non-U.S.-licensed comparator product to address, in part, the requirements under
567 section 351(k)(2)(A) of the PHS Act.”^{22,23} In clinical studies used to support a demonstration of
568 no clinically meaningful differences as a part of demonstrating biosimilarity, the comparator
569 product (whether it is a non-U.S.-licensed product or a U.S.-licensed reference product) serves as
570 a control against which the proposed product is evaluated.

571

572 However, in a switching study that is designed to evaluate the impact of switching or alternating
573 to support a determination of interchangeability, the comparator product plays a different role.
574 Rather than being used only as a control, the comparator product is used in a switching study in
575 both the active switching arm and the control non-switching arm. Switching studies are designed
576 to assess whether one product will affect the immune system’s response to the other product,
577 once the switch occurs, and whether this will result in differences in immunogenicity or PK
578 profiles. Thus, using a non-U.S.-licensed comparator product generally would not be appropriate
579 in a switching study for the following reasons:²⁴

580

581 It is possible that the proposed interchangeable product and the non-U.S.-licensed comparator
582 product have, for example, subtle differences in levels of specific structural features (e.g., acidic
583 variants, deamidations). The immune system reaction in terms of the overall level of antibody
584 produced to each product could be similar, thereby supporting a demonstration of no clinically
585 meaningful differences. Thus, these subtle differences would not preclude a demonstration of

²² See section V on U.S.-licensed reference product and other comparators in the guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*.

²³ See Q.I.8 in the guidance for industry *Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*, which discusses use of a non-U.S.-licensed product to support a demonstration that the proposed product is biosimilar to the reference product.

²⁴ See Q.I.8 in the guidance for industry *Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*, which explains that “[a]t this time, as a scientific matter, it is unlikely that clinical comparisons with a non-U.S.-licensed product would be an adequate basis to support the additional criteria required for a determination of interchangeability with the U.S.-licensed reference product.”

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586 biosimilarity. However, with switching, multiple exposures to each product can prime the
587 immune system to recognize subtle differences in structural features between products, and the
588 overall immune response could be increased under these conditions. This immunologic response
589 is highly dependent on the structural differences between the proposed interchangeable product
590 and the comparator product used in the switching study, in addition to other potential differences
591 between the products (e.g., impurities). Because there may be subtle differences between the
592 U.S.-licensed reference product and the non-U.S.-licensed comparator product, there is
593 uncertainty as to whether the results observed in a switching study using a non-U.S.-licensed
594 comparator product would also be observed if the U.S.-licensed reference product had been used
595 instead.

596

597 Under the BPCI Act, an interchangeable product may be substituted for the reference product
598 without the prescribing health care provider's intervention. There may be multiple versions of a
599 non-U.S.-licensed comparator product on the international market, each approved for use by the
600 relevant national regulatory authority and each with possible subtle differences in levels of
601 structural features from the U.S.-licensed reference product and between each other. The goal of
602 a switching study or studies is to determine a biosimilar product's interchangeability with a
603 reference product that is licensed for use in U.S. clinical settings, thus establishing
604 interchangeability with a product that patients will not receive in the United States would
605 generally not be appropriate.

606

607 For these reasons, FDA strongly recommends that sponsors use a U.S.-licensed reference
608 product in a switching study or studies. Sponsors are encouraged to contact FDA early in the
609 product development process to discuss the design of a switching study, including any proposal
610 to provide adequate scientific justification to support the use of data generated in a switching
611 study using a non-U.S.-licensed comparator product to support a demonstration of
612 interchangeability.

613

614

615 VIII. CONSIDERATIONS FOR DEVELOPING PRESENTATIONS FOR PROPOSED 616 INTERCHANGEABLE PRODUCTS

617

618 The data and information needed to support a demonstration of interchangeability, beyond that
619 needed to demonstrate biosimilarity,²⁵ may also be influenced by the proposed product's
620 presentation.²⁶ This section provides a framework for sponsors to determine the types of data
621 and information related to a proposed presentation that might be necessary to support a
622 demonstration of interchangeability. The considerations described in this section are intended to
623 provide clarity and support flexibility, where appropriate.

624

²⁵ Data and information needed to demonstrate biosimilarity are discussed in section VII of the guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*.

²⁶ For the purposes of this guidance, the term *presentation* means the container closure system and/or delivery device constituent part of the product.

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- Clarity: The framework outlined in this section is designed to provide clear recommendations to guide the development of interchangeable product presentations. Often decisions regarding a presentation are made early in product development. The approach described is intended to reduce potential uncertainty during product development with respect to a proposed presentation and enable sponsors to conduct a product-specific evaluation of their proposed presentation.
- Flexibility: FDA anticipates that sponsors of proposed interchangeable products may develop presentations that have some differences in design from the presentations licensed for the reference product. FDA does not expect that all differences in the design of the presentation of a proposed interchangeable product, when compared to the presentation of a reference product, would negatively impact the appropriate use²⁷ of the product when substituted for the reference product. We intend this section to assist sponsors in tailoring the data and information needed to support a demonstration of interchangeability of their proposed product.

The threshold analyses described in section VIII.B.1.a of this guidance are recommended for all proposed interchangeable products to identify any differences in design between the proposed interchangeable product and the reference product. If there are differences other than minor as observed in the threshold analyses described in section VIII.B, sponsors can use the results from the threshold analyses to determine the need, if any, for additional data or information, such as data and information from a comparative human factors study. FDA expects that such additional studies will likely not be needed for many interchangeable products.

A. General Considerations

When developing a product for licensure as interchangeable under section 351(k) of the PHS Act, it is important that sponsors carefully consider the presentation of the proposed interchangeable product relative to the reference product.²⁸ A sponsor developing an interchangeable product generally should not seek licensure for a presentation for which the reference product is not licensed. For example, if the reference product is only marketed in a vial and a prefilled syringe, a sponsor should not seek licensure for the proposed interchangeable product for a different presentation, such as an auto-injector. A sponsor planning to develop a presentation for which the reference product is not licensed should discuss its proposed presentation with FDA. In such cases, FDA will evaluate whether the proposed presentation could support a demonstration of interchangeability.

As applicable, a general description of the entire container closure system should be provided in the chemistry, manufacturing, and controls (CMC) section of the application. There should be

²⁷ The terms *appropriate use* or *appropriately use* are sometimes used in this section for brevity to refer to use of the proposed interchangeable product in a manner that supports a demonstration of interchangeability under section 351(k) of the PHS Act.

²⁸ See Q.I.4 and Q.I.6 in the guidance for industry *Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*.

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664 complete CMC information for the proposed product, including delivery device constituent part
665 design and development information. The presentation should be shown to be compatible for
666 use with the final formulation of the proposed product through appropriate studies, including, for
667 example, extractable/leachable studies, performance testing, and stability studies. Data and
668 information supporting the appropriate use and performance testing of the delivery device
669 constituent part of the proposed product should be submitted.
670

B. Analysis of Proposed Presentations of Proposed Interchangeable Products

673 The use of a biological product generally involves a sequence of administration steps because
674 biological products are generally injected or infused into the body. In addition, these products
675 are administered by a variety of end users, including health care providers, patients, caregivers,
676 or a combination of these end users.^{29,30} The design of the presentation determines the specific
677 tasks necessary to administer the product. These tasks can vary considerably depending on the
678 type of presentation and its design characteristics. Differences in the design of the container
679 closure system or delivery device constituent part between the proposed interchangeable product
680 and the reference product may be acceptable provided that the design differences are analyzed
681 appropriately and data are provided to demonstrate that the changes do not negatively impact the
682 ability of end users, including patient and caregiver end-user groups, to appropriately use these
683 products when the interchangeable product is substituted for the reference product without the
684 intervention of the prescribing health care provider or additional training before use.
685

686 Because a proposed interchangeable product may be substituted for the reference product
687 without the intervention of the health care provider who prescribed the reference product, a
688 proposed interchangeable product with a differently designed presentation than the reference
689 product may raise uncertainty about whether the difference in presentations would impact the
690 ability of end users, including patients or caregivers, to appropriately use the proposed product.
691 Therefore, FDA recommends that sponsors analyze the presentations of a proposed
692 interchangeable product to identify differences in design compared to the presentations licensed
693 for the reference product using the threshold analysis outlined in this section. These threshold
694 analyses may be used in the development of the proposed presentation to minimize differences
695 between the proposed interchangeable product and the reference product as well as to identify
696 whether additional data, including data from comparative use human factors studies (as
697 described further in this section), may be needed in certain circumstances.
698

699 To conduct the analysis of the presentations of the proposed interchangeable product and
700 reference product for the purposes of identifying differences between the presentations, sponsors
701 should examine the external critical design attributes of the proposed interchangeable product in

²⁹ Administration steps at a high level include the aseptic technique to manipulate the product to prepare it for injection and to ensure that the right dose is administered, followed by a physical manipulation to inject the biologic in the correct site and by the correct route.

³⁰ As a scientific matter, FDA recognizes that the end users of biological products may have different training and expertise, and we provide some technical considerations in this section and in Appendix A for sponsors to consider, as appropriate.

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702 comparison to those of the reference product. External critical design attributes are those
703 features that directly affect the performance of critical tasks³¹ that end users perform to
704 appropriately use or administer the product. To identify these attributes, a sponsor should
705 examine the overall external operating principles of the container closure system or delivery
706 device constituent part by evaluating all the tasks that an end user needs to perform to prepare
707 and administer the product. The external critical design attributes of the product would be those
708 features that end users rely on to perform the tasks identified as critical to the appropriate use of
709 the product. Because these attributes may impact appropriate use of the product, FDA
710 recommends that sponsors consider the external critical design attributes of the reference product
711 as part of their development program for a proposed interchangeable product.
712

713 The technical description of the threshold analysis appears in the next section, which may be of
714 general use for sponsors in the development of proposed interchangeable products. In those
715 circumstances where a threshold analysis indicates that further data may need to be gathered
716 from comparative use human factors studies, Appendix A provides a technical description of
717 comparative use human factors studies intended to support a demonstration of interchangeability.
718

1. Threshold Analyses

721 Three types of threshold analyses can be used in the development program for the purposes of
722 identifying and evaluating differences in design and should be conducted after the presentation
723 of the proposed interchangeable product, including product design and user interface,³² have
724 been finalized by the sponsor and are believed to be representative of the commercial product.
725

726 FDA recommends that sponsors carefully evaluate the risks associated with differences in the
727 container closure system(s) and/or the delivery device constituent part(s) for proposed
728 interchangeable products that may affect the patient or caregiver as the end user,³³ especially
729 because interchangeable products may be substituted for the reference product without the
730 intervention of the prescribing health care provider or additional training before use. The patient
731 or caregiver end-user groups may not receive additional training in such circumstances and may
732 lack the expertise that a health care provider user group is expected to possess. Patient and
733 caregiver end-user groups may be less accustomed to navigating differences in container closure

³¹ For additional information on critical tasks, see Section III.B.1. Critical Tasks in the draft guidance for industry *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development*. When final, this guidance will reflect FDA's current thinking on this topic.

³² The user interface includes all components of the delivery device constituent part with which the user interacts, such as controls and displays (i.e., those parts of the delivery device constituent part that users see, touch, and hear). The user interface also includes the delivery device constituent part labeling, which includes package labels, any instructions for use in user manuals, package inserts, instructions on the delivery device constituent part itself, and any accompanying informational materials. For additional insight, see the guidance for industry and FDA staff *Applying Human Factors and Usability Engineering to Medical Devices*.

³³ For additional information about end-user group considerations, see Section III.B.2. Intended Users and Use Environment in the draft guidance for industry *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development*. When final, this guidance will reflect FDA's current thinking on this topic.

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734 systems and/or delivery device constituent parts for biological products than health care
735 providers. As a result, there is concern that patients or caregivers who encounter different
736 external critical design attributes between the container closure system and/or delivery device
737 constituent part of a reference product and a proposed interchangeable product may be at
738 increased risk for a use-related error that may impact their ability to appropriately use these
739 products.

740

741 a. Types of threshold analyses

742

743 The following three types of analyses are recommended as part of the threshold analyses of
744 proposed product presentation for all proposed interchangeable products:

745

746 i. Labeling comparison

747

748 FDA recommends a side-by-side, line-by-line comparison (between the reference product and
749 the proposed interchangeable product) of the full prescribing information, instructions for use,
750 and descriptions of the container closure systems and/or delivery device constituent parts.

751

752 ii. Comparative task analysis

753

754 FDA recommends that sponsors conduct a comparative task analysis between the reference
755 product and the proposed interchangeable product.³⁴

756

757 iii. Physical comparison of the interchangeable product and the reference
758 product, along with their respective container closure system and/or
759 delivery device constituent part

760

761 FDA recommends that sponsors of proposed interchangeable products acquire the reference
762 product to examine (e.g., visual and tactile examination) the physical features of the reference
763 product and compare them to those of the proposed interchangeable product.

764

765 b. Outcomes of threshold analyses

766

767 After completing the threshold analyses, the following outcomes are possible:

768

769 i. No design differences

770

771 When no differences are identified in the design of the presentation of the proposed
772 interchangeable product and the reference product after the threshold analyses, it is likely that
773 additional data to support the appropriate use of the proposed interchangeable product by the end

³⁴ To conduct a comparative task analysis, sponsors should systematically dissect the use process for each product (i.e., both the proposed interchangeable product and the reference product) and analyze and compare the sequential and simultaneous manual and intellectual activities for end users interacting with both products. FDA recommends that sponsors analyze the differences, with the goal of characterizing the potential for use error. Also see the American National Standards Institute/Association for the Advancement of Medical Instrumentation HE75, 2009(R)2013 Human Factor Engineering—Design of Medical Devices. The standard can be accessed at <http://www.aami.org/productpublications/ProductDetail.aspx?ItemNumber=916>.

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774 users, including data from comparative use human factors studies, will not be necessary to
775 support licensure as an interchangeable product. The sponsor should provide any analyses
776 comparing the presentations for FDA's review and concurrence.

777

778 ii. Differences in design

779

780 If differences are identified between the design of the presentations of the proposed
781 interchangeable product and the reference product, the sponsor should focus on whether the
782 difference(s) involves an external critical design attribute that can negatively impact appropriate
783 use by the patient and caregiver end-user groups and should seek to establish and categorize the
784 differences as follows:

785

- 786 • Minor design differences: FDA views a design difference in product presentation as
787 minor if the differences in the user interface of the proposed interchangeable product,
788 in comparison to the user interface of the reference product, do not affect an external
789 critical design attribute. Minor differences in design are likely to be viewed by FDA
790 as acceptable provided that the data and information submitted by the sponsor
791 demonstrate that the differences are in fact minor. For example, such data and
792 information may be collected from thorough threshold analyses (described in
793 sectionVIII.B.1.a of this guidance) that demonstrate that the differences in design do
794 not involve an external critical design attribute that could negatively impact
795 appropriate use. Similarly, for those products that would be expected to be
796 administered only by a health care provider, the risks associated with substitution
797 may be adequately addressed through threshold analyses rather than a comparative
798 use human factors study. As mentioned previously, patient and caregiver end-user
799 groups may be less accustomed to navigating differences in container closure systems
800 and/or delivery device constituent parts for biological products than health care
801 providers. The sponsor should provide this data and information for FDA's review
802 and concurrence.
- 803 • Other design differences: FDA may not view a design difference as minor if any
804 aspect of the threshold analyses suggests that differences in the design of the
805 presentation of the proposed interchangeable product as compared to the reference
806 product *may* impact an external critical design attribute that involves patient use or
807 caregiver administration of the product. In such cases, the sponsor may consider
808 modifying the design of the proposed presentation to minimize differences from the
809 reference product, which could reduce the data that might be needed to support a
810 demonstration of interchangeability.³⁵ Alternatively, if such differences are present

³⁵ FDA recognizes that, in certain circumstances, a sponsor may elect to retain a difference in design of an interchangeable product compared to the reference product to reduce difficulty with use or to minimize risk associated with the design of the reference product's presentation. FDA generally encourages the optimization of the design of the delivery device constituent part to enhance the safety of the product. However, there may be circumstances where an interchangeable product may be substituted for the reference product without additional end-user training. Thus, it is important that sponsors identify differences between their proposed presentation and the reference product's presentation, as described in this guidance, including identifying any differences intended to optimize the design of the delivery device constituent part to enhance the safety of the product. The sponsor should also characterize any identified differences in design that may impact the end user's ability (particularly patients and

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811 in the final design of the presentation of the proposed interchangeable product, FDA
812 recommends that sponsors provide appropriate data from additional studies, such as
813 from a comparative use human factors study, to address whether such differences
814 might negatively affect the appropriate use of the biological product in circumstances
815 where the interchangeable product is substituted for the reference product. The data
816 from additional studies should seek to characterize whether the difference(s) could
817 negatively affect the appropriate use of the products by patients and caregivers (see
818 section VIII.B.2 of this guidance for types of studies). Based on the results of
819 additional studies, FDA may or may not determine that the design difference between
820 the presentation of the proposed interchangeable product and the reference product is
821 acceptable for a proposed interchangeable product.
822

823 2. *Studies to Evaluate Differences That May Not Be Minor as Observed in Threshold* 824 *Analyses*

825 If the threshold analyses determine that a design difference may not be minor, as described in
826 section VIII.B.1.b.ii of this guidance, sufficient evidence should be provided to permit FDA to
827 evaluate the design difference for purposes of interchangeability. Alternatively, as mentioned
828 previously, the sponsor may consider modifying the design of the proposed presentation to
829 minimize differences from the reference product, which could reduce the data that might be
830 needed to support a demonstration of interchangeability. However, if differences that may not be
831 minor are present in the final design of the presentation of the proposed interchangeable product,
832 FDA recommends that sponsors provide appropriate data from additional studies to support these
833 differences. Such data may be gathered in a focused comparative use human factors study that
834 evaluates the critical tasks related to the external critical design attributes that are found to be
835 different or to focus on the patient and caregiver end-user group(s) that are most likely to be
836 negatively impacted by the differences in the design of the presentation of the proposed
837 interchangeable product and the reference product.
838

839 a. Comparative use human factors studies

840 Comparative use human factors studies may be needed to provide the evidence necessary to
841 assess whether differences that may not be minor in the design of the presentation of the
842 proposed interchangeable product prevent licensure of the proposed product as interchangeable
843 with the reference product. The objective of the comparative use human factors studies
844 described in this guidance is to assess any differences in the use error rate between the reference
845 product and the proposed interchangeable product. This objective differs from the objective of
846 human factors validation studies, which are conducted to evaluate how a product's user interface
847 supports safe and effective use; such studies are not designed to assess differences in use error
848 rates between two products. Therefore, the human factors validation studies described in the
849 guidance for industry and FDA staff *Applying Human Factors and Usability Engineering to*
850 *Medical Devices* generally do not apply when evaluating interchangeability.
851

852

853 caregivers) to appropriately use an interchangeable product when substituted for the reference product. (See
854 section VIII.B.2 of this guidance.)

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854 See Appendix A of this guidance for considerations for comparative use human factors studies
855 (if needed) to evaluate differences that may not be minor, as observed in threshold analyses.

856

857 b. Additional studies

858

859 The need for additional data or information to support a presentation beyond what is described in
860 this guidance may depend on a risk-based analysis and will be determined on a case-by-case
861 basis. Additional studies such as comparative in vivo or in vitro performance testing may be
862 warranted to support a demonstration of interchangeability under section 351(k) of the PHS
863 Act.³⁶ FDA recommends that sponsors define specifications for each testing parameter before
864 studies are initiated. Sponsors are encouraged to discuss appropriate testing with FDA as early
865 during product development as feasible.

866

867

868 **IX. POSTMARKETING SAFETY MONITORING CONSIDERATIONS**

869

870 Robust postmarketing safety monitoring is an important component in ensuring the safety and
871 effectiveness of biological products, including biosimilar and interchangeable products.

872

873 Postmarketing safety monitoring for interchangeable products should first take into consideration
874 any particular safety or effectiveness concerns associated with the use of the reference product
875 and its class, the proposed interchangeable product in its development and clinical use (if
876 marketed outside the United States), the specific condition of use and patient population, and
877 patient exposure in the interchangeability development program. Postmarketing safety
878 monitoring for an interchangeable product should also have adequate pharmacovigilance
879 mechanisms in place.³⁷ Rare but potentially serious safety risks may not be detected during
880 preapproval clinical testing because the size of the population exposed likely will not be large
881 enough to assess rare events. In particular cases, such risks may need to be evaluated through
882 postmarketing surveillance or studies. In addition, as with any other biological product, FDA
883 may require a postmarketing study or a clinical trial to evaluate certain safety risks.³⁸

884

885 Because some aspects of postmarketing safety monitoring are product-specific and dependent
886 upon the risk that is the focus of monitoring, FDA encourages sponsors to consult with
887 appropriate FDA divisions to discuss the sponsor's proposed approach to postmarketing safety
888 monitoring.

889

890

³⁶ Comparative in vivo or in vitro performance testing may include the critical elements in establishing dose accuracy; for example, extended needle length, needle integrity, activation force, dispensing time, and dispensing volume. Additional types of performance specification testing, such as activation force, breakloose force, extrusion force, needle gauge, and needle protrusion, may need to be considered as well.

³⁷ For general pharmacovigilance considerations, see the guidance for industry *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment and the guidance for industry Postmarketing Adverse Experience Reporting for Human Drug and Licensed Biological Products: Clarification of What to Report*.

³⁸ See section 505(o)(3) and 505(p)(1)(A)(ii) of the Federal Food, Drug, and Cosmetic Act.

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891 **APPENDIX A: COMPARATIVE USE HUMAN FACTORS STUDIES**

892
893 Considerations for Comparative Use Human Factors Studies, if needed, to evaluate differences
894 that may not be minor as observed in threshold analyses:

895
896 **1. Study Design Considerations**

897
898 To support a demonstration of interchangeability under section 351(k) of the PHS Act, a
899 comparative use human factors study should be designed to provide data supporting that the use
900 error rate for the proposed interchangeable product is not worse than the use error rate for the
901 reference product when used by patients and caregivers (as applicable) in representative use
902 scenarios and use environments. The comparative use human factors studies described in this
903 guidance would generally be simulated-use studies³⁹ where the participants, who are
904 representative of the patients and caregivers, are asked to simulate the use of the product
905 presentations (container closure systems and/or delivery device constituent parts) without
906 actually administering the product.

907
908 For many aspects of demonstrating interchangeability under section 351(k) of the PHS Act, data
909 is best collected using an equivalence study design. For example, it would be unlikely for FDA
910 to determine that a proposed product is interchangeable with a reference product if data showed
911 it to have lower or higher exposure than the reference product. In such cases, there could be a
912 negative impact to the patient associated with a substantial deviation from equivalence.
913 However, for the purpose of the comparative use human factors studies described in this
914 appendix, the risks associated with container closure systems and delivery device constituent
915 parts are derived from errors that occur in using the container closure system and/or delivery
916 device constituent part. FDA would generally accept a proposed interchangeable product that
917 had the same rates of error as the reference product, as demonstrated by an adequately designed
918 comparative use human factors study or studies. However, we also recognize that lower error
919 rates for a proposed interchangeable product compared to error rates for the reference product
920 would likely not be considered to negatively impact the interchangeability assessment.
921 Therefore, lower bounds on error rates are generally not necessary in comparative use human
922 factors studies described in this appendix. For this reason, instead of using equivalence designs,
923 noninferiority (NI) study designs are generally appropriate in such situations. NI tests comparing
924 use of the presentation of a proposed interchangeable product to that of the reference product are
925 similar to usual statistical tests for a difference, but translated to account for allowable
926 differences in design between the presentation of the proposed interchangeable product and the
927 reference product.

928
929 In comparing pharmaceutical products, NI tests are often conducted to indirectly demonstrate
930 that a proposed product is more efficacious than a placebo. A standard way of approaching this
931 goal is to fix an NI margin (referred to as d in this appendix) at some fraction of the difference

³⁹ For more information on simulation techniques, see Section D.1. Human Factors Simulated Use Validation Studies in the draft guidance for industry *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development*. When final, this guidance will reflect FDA's current thinking on this topic.

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932 between the placebo effect and the effect of the proposed product. Showing the effect of the
933 proposed product to be significantly better than the margin demonstrates NI. The draft guidance
934 for industry *Non-Inferiority Clinical Trials* discusses meta-analyses and margin selection in
935 detail.⁴⁰ A comparative human factors study with an NI design for the purpose of demonstrating
936 interchangeability under section 351(k) of the PHS Act will typically be less complicated than
937 those described in the guidance on NI clinical trials because the endpoints of these NI studies
938 will not be dependent on therapy and the placebo effect will not be a confounding factor.
939

940 The choice of comparative use human factors study endpoint(s) will depend on the nature of the
941 presentation being evaluated and the associated differences between presentation of the proposed
942 interchangeable product and the reference product identified in the threshold analyses. Although
943 there may be many possible endpoints, a study evaluating performance of a critical task can often
944 be reduced to a binary endpoint that considers whether or not the end user makes an error in
945 performing the task. One possible endpoint for such a study may be the rates of errors observed
946 when using the presentations of the proposed interchangeable product and the reference product.
947 In this guidance, we show ER_{IP} and ER_{RP} as error rates observed when using the presentation
948 associated with the proposed interchangeable product and that of the reference product,
949 respectively.

950
951 Using the result of the threshold analyses described earlier as a guide, a risk assessment should
952 be done to identify the external critical design attributes, end-user group(s), use scenarios, and
953 use environments on which to focus the comparative use human factors study intended to support
954 a demonstration of interchangeability. FDA recommends that patient and caregiver end users (as
955 applicable) of the reference product be considered for inclusion in the comparative use human
956 factors study. The risk assessment should explore risks for the various subgroups of the current
957 patient and caregiver end-user groups and may identify an appropriate subpopulation on which to
958 focus the comparative use human factors study. For example, in some cases, the risk assessment
959 may determine that only a certain patient subpopulation (or subpopulations) is likely to
960 experience difficulty administering the product, and thus the comparative use human factors
961 study may be most appropriately focused on the identified patient subpopulation(s).
962

963 The goal of a comparative use human factors study intended to support a demonstration of
964 interchangeability with an NI design is to demonstrate that ER_{IP} is no greater than $ER_{RP} + d$,
965 where d is some acceptable deviance above ER_{RP} . In determining the margin d , the variability in
966 ER_{RP} should be considered as well as the risk any difference in outcomes will pose to patients.
967 The results of the risk assessment should be considered when determining the NI margin (d)
968 between ER_{RP} and ER_{IP} .
969

970 An example of a simple and direct approach to an NI test comparing ER_{IP} and ER_{RP} can be
971 summarized as follows:
972

- 973 • Determine the allowable margin (d) by which ER_{IP} could exceed ER_{RP} .

⁴⁰ For additional insight, see the draft guidance for industry *Non-Inferiority Clinical Trials*. When final, this guidance will reflect FDA's current thinking on this topic.

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974 • Calculate the study sample size, considering assumed error rates and d .

975 • Observe error rates for the critical task(s) during the experiment.

976 • Perform the statistical hypothesis test:

977 ○ $H_0: ER_{IP} - ER_{RP} > d$

978 ○ $H_A: ER_{IP} - ER_{RP} \leq d$

979 Rejecting the null hypothesis (H_0) in favor of the alternative hypothesis (H_A) supports the claim
980 of NI as defined by d .

981 Typically, the acceptable Type I error probability (α) will be set at 5%.

982
983 The NI test may be performed by comparing the upper bound of the appropriate confidence
984 interval level for the difference in event rates to d . If the upper bound is less than d , NI is
985 demonstrated.

986
987 Paired designs and parallel designs are appropriate approaches to the NI studies discussed in this
988 appendix. A paired design in which each end user uses both presentations and acts as his or her
989 own control will generally be applicable and more efficient with respect to resources than a
990 parallel design. Parallel group designs in which end users are randomized to groups using one or
991 the other presentation are also viable in situations where paired designs are not possible.
992 Sponsors are advised to propose and discuss study designs with FDA before initiating studies.

2. Sample Size Considerations

993
994
995 Sample sizes for a comparative use human factors study should be adequate to support a
996 demonstration of interchangeability. Sample sizes needed to adequately compare the
997 presentations of the reference product and the proposed interchangeable product may be larger
998 than those described generally in the human factors study literature. In general, small sample
1000 sizes are likely to be inadequate in this context because the goals of the comparative use human
1001 factors studies to support a demonstration of interchangeability may be different than the goals of
1002 typical human factors/usability studies discussed in the literature and certain FDA guidances.
1003 The literature on human factors studies holds a variety of opinions with respect to sample sizes.
1004 Some references dedicated to qualitative, non-comparative human factors studies suggest small
1005 sample sizes (5 to 25 participants), while other studies suggest that greater numbers of test
1006 subjects should be included.^{41,42,43}

⁴¹ Faulkner, L, 2003, Beyond the five-user assumption: Benefits of increased sample sizes in usability testing, *Behavior Research Methods, Instruments, and Computers*, 35(3), 379–383.

⁴² Nielsen, J, 2000, Why You Only Need to Test With 5 Users, Jakob Nielsen's Alertbox, Retrieved October 13, 2015, from <http://www.useit.com/alertbox/20000319.html>.

⁴³ Spool, J, Schroeder, W, 2001, Testing web sites: Five users is nowhere near enough, in CHI 2001 Extended Abstracts (p. 285-286), New York: ACM Press.

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1007
1008 The comparative use human factors studies described in this appendix are intended to ensure that
1009 design differences other than minor design differences found in the threshold analyses (described
1010 in section VIII.B.1 of the guidance) do not preclude a demonstration of interchangeability under
1011 section 351(k) of the PHS Act. Thus, as a scientific matter, a larger sample size may be
1012 necessary. Consider, for example, a failure in a critical task that can result in under-dosing that
1013 has a negative impact on a patient. If a study of 50 users showed no such failures, the upper
1014 bound of the 90% confidence interval for the error rate would be 0.058. This means that an error
1015 rate of approximately 6% at a reasonable confidence level could not be ruled out. If 50 subjects
1016 were asked to operate two delivery device constituent parts, one being the reference product and
1017 another being the proposed interchangeable product, and no subject failed using either delivery
1018 device constituent part, the 90% confidence interval for the difference in error rates would be
1019 (-0.051, 0.051). Although the observed difference in error rates is zero, such a demonstration
1020 does not rule out a 5% difference in error rates at the 90% confidence level. Putting these
1021 numbers into the context of the under-dosing example, the question is whether it is acceptable to
1022 expect up to 58 out of 1,000 users to be under-dosed. The risk associated with the specific error
1023 in question will determine the acceptability of error rates. In some cases, a 6% error rate or a 5%
1024 difference in error rates would be untenable, even though there could be other contexts in which
1025 such rates or differences would be acceptable. This example illustrates the importance of the risk
1026 analysis portion of the comparative use human factors study design, as well as the importance of
1027 properly sizing the study.
1028
1029 If extremely small error rates are expected, an adaptive design may be used to minimize sample
1030 size, while allowing for an adequate sample size if error rates are higher than initially assumed.
1031 Group sequential designs that are designed to stop early or a study design that adapts sample size
1032 may be considered. Consult the appropriate FDA guidance documents for detailed advice on
1033 designing studies using adaptive designs.⁴⁴
1034

⁴⁴ For detailed advice on designing studies using adaptive designs, see the draft guidances for industry *Adaptive Designs for Medical Device Clinical Studies* and *Adaptive Design Clinical Trials for Drugs and Biologics*. When final, these guidances will reflect FDA's current thinking on this topic.